February 12, 2018

Ms. Monet Vela
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
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Sacramento, California 95812-4010
Email: monet.vela@oehha.ca.gov

Submitted via the Comments Submission Portal: https://oehha.ca.gov/comments

Re: Notice of Proposed Rulemaking Title 27, California Code of Regulations Amendment to Section 12705 Specific Regulatory Levels Posing No Significant Risk: Bromochloroacetic Acid.

Dear Ms. Vela:

The American Chemistry Council[1] (ACC) Chlorine Chemistry Division[2] appreciates this opportunity to provide comments to the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed rulemaking to adopt a Proposition 65 No Significant Risk Level (NSRL) for bromochloroacetic acid of 0.70 micrograms/day[3] and "Initial Statement of Reasons" (ISOR) document[4] for the proposed amendment.

Millions of lives have been saved and countless illnesses avoided since the inception of continuous chlorine use in conjunction with filtration in water treatment over 100 years ago,[5] and the majority of U.S. community water systems still rely on chlorine or a chlorine-

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[1] ACC represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a $768 billion enterprise and a key element of the nation's economy. It is among the largest exports in the nation, accounting for 14 percent of all U.S. goods exports. Chemistry companies are among the largest investors in research and development, investing $91 billion in 2016.

[2] The Chlorine Chemistry Division represents the major producers and users of chlorine in North America and works to promote and protect the sustainability of chlorine chemistry processes, products and applications.

[3] https://oehha.ca.gov/proposition-65/crnr/notice-proposed-rulemaking-title-27-california-code-regulations-amendment-11.

[4] https://oehha.ca.gov/media/downloads/crnr/isorbromochloroaceticacid122917.pdf.

[5] See review by McGuire, M.J. 2013. The Chlorine Revolution: Water Disinfection and the Fight to Save Lives. AWWA: Denver, Colorado.

based disinfection process to protect their consumers.[6] A wide variety of organic and inorganic disinfection byproducts (DBPs), including bromochloroacetic acid, can be formed unintentionally at low levels when chlorine and other disinfectants react with naturally occurring organic matter in raw (natural) sources of drinking water. As the World Health Organization strongly cautions: "In attempting to control DBP concentrations, it is of paramount importance that the efficiency of disinfection is not compromised and that a suitable residual level of disinfectant is maintained throughout the distribution system."[7]

Given the clear public health importance of chlorine and chlorine-based disinfection, it is of critical importance that the proposed NSRL for bromochloroacetic acid reflect the use of best available science for its derivation.

The attached comments, prepared by Jay Murray, PhD, DABT, detail ACC's technical concerns with the proposed NSRL—including that OEHHA should explicitly state that the NSRL for bromochloroacetic acid does not specifically consider the role of chlorine-based disinfection, and that an alternative risk level would be appropriate when bromochloroacetic acid results from chlorine disinfection.

Should you have questions or would like to discuss these comments, please contact me at judith_nordgren@americanchemistry.com or Mark Gibson at mark_gibson@americanchemistry.com.

Respectfully,

Judith Nordgren

Judith Nordgren
Managing Director, Chlorine Chemistry Division

<u>Attachment</u>:
Comments on the Proposed Proposition 65 No Significant Risk Level (NSRL) for Bromochloroacetic Acid (February 7, 2018)

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[6] See American Chemistry Council. 2016. Drinking Water Chlorination: A Review of U.S. Disinfection Practices and Issues, https://chlorine.americanchemistry.com/Chlorine-Benefits/Safe-Water/Disinfection-Practices.pdf.

[7] WHO (2011), Guidelines for Drinking-water Quality, 4th Edition. WHO Press: Geneva, Switzerland, p. 173, http://www.who.int/water_sanitation_health/publications/2011/dwq_guidelines/en/.

Comments on the Proposed Proposition 65 No Significant Risk Level (NSRL) for Bromochloroacetic Acid

February 7, 2018

Prepared for:

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Prepared by:

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February 7, 2018

I was asked by the American Chemistry Council (ACC) to review the Office of Environmental Health Hazard Assessment's (OEHHA) "Notice of Proposed Rulemaking Title 27, California Code of Regulations Amendment to Section 12705 Specific Regulatory Levels Posing No Significant Risk: Bromochloroacetic Acid"[1], and the associated Initial Statement of Reasons (ISOR) for the proposed No Significant Risk Level (NSRL) for bromochloroacetic acid.[2] The following comments are provided pursuant to OEHHA's request for public comments in response to these documents.

1. **OEHHA should specifically state that the NSRL for bromochloroacetic acid does not consider the role of chlorine-based disinfection, and that an alternative risk level would be appropriate when bromochloroacetic acid results from chlorine disinfection.**

The NSRL proposed for bromochloroacetic acid does not evaluate the propriety of an alternative risk level, as supported by Section 25703(b) of the Proposition 65 regulations. Section 25703(b) states:

> "b) For chemicals assessed in accordance with this section, the risk level which represents no significant risk shall be one which is calculated to result in one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure at the level in question, ***except where sound considerations of public health support an alternative level***, as, for example:
>
> > (1) where chemicals in food are produced by cooking necessary to render the food palatable or to avoid microbiological contamination; or
> >
> > (2) ***where chlorine disinfection in compliance with all applicable state and federal safety standards is necessary to comply with sanitation requirements***; or

[1] https://oehha.ca.gov/proposition-65/crnr/notice-proposed-rulemaking-title-27-california-code-regulations-amendment-11

[2] https://oehha.ca.gov/media/downloads/crnr/isorbromochloroaceticacid122917.pdf

> (3) where a clean-up and resulting discharge is ordered and supervised by an appropriate governmental agency or court of competent jurisdiction." [emphases added]

Bromochloroacetic acid is recognized as a disinfection by-product of chlorine disinfection of drinking water. The NTP cancer bioassay of bromochloroacetic acid (the pivotal study used for the proposed NSRL) states: "Bromochloroacetic acid is a water disinfection by-product."[3] In fact, bromochloroacetic acid was nominated for testing by the NTP by the United States Environmental Protection Agency (USEPA) because of the widespread human exposure to this water disinfection by-product.

Bromochloroacetic acid is a compelling example of a chemical that merits an alternative risk level. Chlorine-based disinfection is critical to providing safe drinking water. Using an alternative risk level (e.g., 10^{-4} or 10^{-3}) would result in a significant increase in the NSRL (e.g., a 10-fold increase in the NSRL at an alternative risk level of 10^{-4}). The ISOR and the regulation should mention the possibility and propriety of an alternative risk level for this chlorine disinfection by-product.

Furthermore, this is not a theoretical concern. At the proposed NSRL of 0.70 micrograms/day, consumption of 2 L of water (i.e., the default consumption of drinking water under Proposition 65) containing more than 0.35 micrograms/L (0.35 ppb) of bromochloroacetic acid would provide an exposure in excess of the NSRL. Based on limited data, it does not appear that drinking water levels of bromochloroacetic acid are comfortably below 0.35 micrograms/L. Of note, the Introduction section of the NTP cancer bioassay report (TR 549) states:

> "Levels of haloacetic acids in drinking water are regulated by the USEPA (40 CFR, § 141.64). Under the disinfection by-products rule, the sum of the concentrations of monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, monobromoacetic acid,

[3] National Toxicology Program (NTP, 2009). Toxicology and Carcinogenesis Studies of Bromochloroacetic Acid (CAS No. 5589-96-8) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). NTP Technical Report Series No. 549. NIH Publication No. 09-5890. US Department of Health and Human Services, NTP, Research Triangle Park, NC, NC, p. 7

> and dibromoacetic acid is limited to 60 μg/L (60 ppb). This level is believed to reduce risks from cancer as well as reproductive and developmental toxicity. However, bromochloroacetic acid is not included in the five haloacetic acids regulated by the USEPA under the current disinfection by-products rule. A nationwide study of disinfection by-product occurrence in diverse geographic regions of the United States was conducted between October 2000 and April 2002 (Weinberg et al., 2002). In this study, 12 water treatment plants that had different source water quality and bromide levels and that employed the major disinfectants chlorine, chloramines, ozone, and chlorine dioxide were sampled quarterly. Concentrations of bromochloroacetic acid ranged up to 19 µg/L in finished water samples and in the distribution systems."[4]

These data illustrate why it is important for OEHHA to explicitly state that an alternative risk level for developing a NSRL for bromochloroacetic acid would be appropriate in those circumstances where section 25703(b) applies.

2. **The ISOR should acknowledge the significant uncertainty in estimating a cancer slope factor based on liver tumor data in male and female mice where every dose group of bromochloroacetic acid had a tumor response in the range of 90% to 100%.**

The proposed NSRL of 0.70 micrograms per day is based on the incidence of combined liver tumors in in male and female mice. To develop a cancer slope factor for female mice, the ISOR notes that the two top dose groups had to be removed during the modeling process "in order to achieve sufficient goodness of fit." This is because the liver tumor response was essentially maxed out at all three dose levels. The incidences of liver tumors among the female mice were 31/45, 49/50, 46/49, and 46/48 at 0, 15, 30, and 60 mg/kg bw/day of bromochloroacetic acid, respectively. When all three dose levels were included, the data failed to meet all of the USEPA's statistical criteria for acceptability. Even when the top dose was excluded, the data did not meet US EPA's statistical criteria for acceptability. As OEHHA determined, it is not

[4] NTP (2009), p. 26.

possible to generate a cancer slope factor for bromochloroacetic acid based on liver tumors in female mice unless both the top and middle dose levels are excluded from the calculations.

In comparison, in male mice, all three dose levels were included because the data fit the model. The incidences of liver tumors in the male mice were 35/50, 45/50. 49/49, and 50/50 at 0, 25, 50, and 90 mg/kg bw/day, respectively. Similar to the findings in female mice, the range of liver tumor responses in male mice was high at all three dose levels (i.e., 90% to 100%). But, because the tumor incidence increased slightly across these three ascending dose levels, the data fit the model. In the female mice, because the incidence of liver tumors was highest at the low dose, the data did not fit the model until the middle and high dose were excluded. In reality, there may be very little difference in tumor response in males and females within this dose range. The small difference in liver tumor rates among the three groups exposed to bromochloroacetic acid could easily be attributed to random variation at dose levels where the tumor response has plateaued. In other words, the difference in tumor response and cancer slope factor between the male and female mice may have been due to random variation in tumor response at a dose range producing a maximal tumor response. Of note, OEHHA used liver tumor data in both male and female mice to derive the NSRL, and the possibility that the slight gender difference in the liver tumor response in the high dose range may be due to chance provides an additional rationale to base the cancer slope factor on the average of the male and female mouse values.

The ISOR should acknowledge there is an inherent problem with predicting a 5% tumor response dose from a set of data where every dose level of the test material had a tumor response in the range of 90% to 100%. The ISOR should state that this is a weak set of data for purposes of modeling a cancer slope factor. The data give no indication of the shape of the dose-level at a tumor response rate below 90%. As a result, there is considerable uncertainty in the estimated BMDL05 for liver tumors. It is important to note this uncertainty in the ISOR.

3. **The NSRL should be based on a BMDL10 rather than a BMDL05.**

The US EPA software employed by OEHHA to calculate the BMDL uses a default BMDL10. OEHHA did not explain its decision to depart from this default approach. Ideally, the tumor response data is within or close to the BMDL value. Since the tumor rate was so high at all three dose levels, it would be more appropriate to use a BMDL10, rather than a BMDL05. Using the BMDL10 would have resulted in a slightly higher NSRL. For example, the cancer slope factor in female mice based on a BMDL10 and a BMDL05 (excluding the top two doses) is 0.317 and 0.325 per mg/kg/day, respectively.

OEHHA departs from the traditional method of expressing the tumor incidence (i.e., using the total number of animals in the group in the denominator). Instead, OEHHA uses in the denominator the number of animals alive at the time of the occurrence of the first tumor. Because of this difference, the tumor incidences used by OEHHA to calculate the NSRL differ from those presented by the NTP in its cancer bioassay. This practice is concerning, is not adequately justified, and should be the subject of further discussion.

4. **The ISOR should acknowledge that this risk assessment assumes mouse liver tumors are relevant to humans.**

The human relevance of the mouse liver tumors is debatable. The mouse liver is a common target site for the carcinogenic effects of the trihalomethanes and haloacetic acids that occur in drinking water as disinfection by-products. The ISOR should state that mouse liver tumors were conservatively assumed to be relevant to humans for purposes of determining the NSRL.

5. **The ISOR should delete the sentence that states: "There are no principles or assumptions scientifically more appropriate, based on the available data, than this approach."**

There is a substantial body of scientific evidence that certain types of liver tumors observed in mice are not relevant to humans. OEHHA has not conducted a deep and thorough evaluation of the mode of action and human relevance of the mouse liver tumors induced by bromochloroacetic acid. In comparison, the ISOR states: "Based on consideration of the available mechanistic information on bromochloroacetic acid and the above conclusions reached by IARC…a multistage model is applied to derive a cancer potency estimate, following the guidance in Section 25703. There are no principles or assumptions scientifically more appropriate, based on the available data, than this approach."[5] This last sentence is not correct, and the sentence is not necessary. Furthermore, the sentence may be misconstrued to indicate that an alternative risk level is not possible or appropriate. For these reasons, OEHHA should delete this sentence.

6. The ISOR should mention the underlying uncertainty of estimating the human cancer slope factor by using the default allometric scaling factor in the Proposition 65 regulations.

The ISOR states: "Human cancer potency is estimated by an interspecies scaling procedure. According to Section 25703(a)(6), dose in units of mg per kg body weight scaled to the three-quarters power is assumed to produce the same degree of effect in different species in the absence of information indicating otherwise." In effect, the default interspecies scaling procedure assumes that larger animals with greater body surface area are more susceptible to carcinogens than smaller animals with lesser body surface area. Based on this approach, humans are assumed to be approximately 6 times more sensitive than mice to the potential carcinogenicity of all carcinogens, including bromochloroacetic acid. Based on the same allometric scaling approach, rats are assumed to be 2 times more sensitive than mice to the potential carcinogenicity of bromochloroacetic acid, but the data show the opposite (i.e., the cancer slope factor based on the mouse data is greater than the cancer slope factor based on rat data). The default allometric scaling factor approach in the regulations is conservative, and it is worth mentioning that in the case of rats, the mouse data over-predicted the carcinogenicity of bromochloroacetic acid.

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[5] ISOR (2017), p. 4.